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THE NATH LAW GROUP 112 South West Street Alexandria, VA 22314			EXAMINER WELTER, RACHAEL E	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary****Application No.**

09/673,872

**Applicant(s)**

WAI-CHIU SO ET AL.

**Examiner**

RACHAEL E. WELTER

**Art Unit**

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**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 6/20/08.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4, 6, 8, 10-16, 19-21, 23-24, 26, 29-40, 43-53, 56-73, 76-97, 100-112, 114-125, 128-138 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 8, 12-16, 19-21, 23-24, 26, 29-33, 36-40, 43-44, 112, 114, 118-125, 128, 131-133, 135-138 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

Continuation of Disposition of Claims: Claims withdrawn from consideration are 10,11,34,35,45-53,56-73,76-97,100-111,115-117,129,130 and 134.

## DETAILED ACTION

### *Status*

Claims 1-4, 6, 8, 10-16, 19-21, 23-24, 26, 29-40, 43-53, 56-73, 76-97, 100-112, 114-125, 128-138 are pending in this application. Claims **1-4, 6, 8, 12-16, 19-21, 23-24, 26, 29-33, 36-40, 43-44, 112, 114, 118-125, 128, 131-133, 135-138** are directed to the elected species. Claims 10-11, 34-35, 45-53, 56-73, 76-97, 100-111, 115-117, 129-130, 134 are withdrawn as being directed to the nonelected species. Claims 5, 7, 9, 17-18, 22, 25, 27-28, 41-42, 54-55, 74-75, 98-99, 113, 126-127 stand cancelled.

### *Acknowledgements*

Receipt of the amendment and remarks/arguments filed on June 20, 2008 is acknowledged.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

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4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1-4, 6, 8, 12, 13, 15-16, 19-21, 23-24, 26, 29, 112, 114, 118-120, 121-125, 128, 131-132, 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 88/01863 to Peck et al in view of WO 97/12602 to Weiner et al or Yu et al (EP0273202) respectively.**

Peck teaches a quick breaking foam to treat baldness comprising either (a) 1-5% minoxidil; (b) 10-50% propylene glycol; (c) 30-75% alcohol; (d) 0.5-10% emulsifier and/or surfactant; (e) 0.1-5% hydroxypropyl methylcellulose; and (f) 10-50% water wherein the composition is actuated with a propellant. See page 2. Peck teaches the minoxidil may be selected from any known analog. Peck teaches skin penetrates including alcohol such as dodecanol and oleyl alcohol. See page 5. Peck teaches various surfactants in the composition including Tween 80 (polysorbate) and Span 60 to improve the stability of the composition. See page 6, lines 20-25. Peck teaches the use of minoxidil or a salt thereof. See page 5, lines 25-30.

Peck does not teach the instant acid salt.

WO teaches a topical composition for minoxidil and teaches minoxidil is not soluble in water, acetone, and ethyl acetate and although the alcohol based solutions of minoxidil have only some penetration. See page 2. WO teaches modifying the solubility of the active in an aqueous solution by making it more hydrophilic without changing the active agent's therapeutic properties. The active agent that is more hydrophilic has improved penetration through the hair follicle. WO teaches modifying by reacting it with a hydroxy organic acid such as lactic acid. See page 3 and 4.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help the minoxidil dissolve in

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the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

It is would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Peck and WO and utilize the instant minoxidil acid salt. One would have been motivated to do so since WO teaches this addition to yield a hydrophilic compound, allows for better penetration into the hair follicles. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teaching of Peck and Yu et al and utilize the instant acid. One would be motivated to do so Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid to form a minoxidil acid salt for enhanced penetration of minoxidil into the hair follicle.

Regarding the recitation of "at least 5%", Peck teaches minoxidil in an amount of 1-5%. "At least 5%" includes 5.00001%, 5.001%, etc, which is considered obvious over the prior art's "5%". It would have been obvious to a skilled artisan at the time the invention was made to manipulate the concentration of minoxidil during routine optimization.

Regarding the recitation "approximately 7.5 to 12%", the examiner directs applicant's attention to MPEP 2111.01. Applicant has not defined the term "approximately" to mean exactly. Thus, "approximately 7.5%" is given latitude.

Regarding the instantly claimed ratio of ethanol to water, Peck sets forth a general range of components wherein the alcohol is utilized in an amount of 30-75% and water from 10-50%, thus it is within the skill of an artisan to look at the guidance provided by Peck and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

### ***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues that the examiner has not established a prima facie case of obviousness. Applicant argues that the PTO must satisfy three requirements. The PTO must provide a reason to combine the elements in the prior art, a reasonable expectation of success, and the reference or combination of references should teach all the claimed limitations. Applicant argues that a prima facie case of obviousness has not been established because Peck et al and Weiner et al /Yu et al fail to teach or suggest all the limitations of the claims. Applicant further argues that there is no motivation to modify Peck et al to incorporate an acid salt since Weiner teaches away from a minoxidil acid salt.

As acknowledged by applicant, the critical question in establishing a prima facie obviousness case is to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does..." KSR International Co. V. Teleflex Inc., 550 U.S. -, 82 USPQ2d 1385 (2007). In the instant case and as set forth in the rejection, Weiner teaches this addition to yield a hydrophilic compound, which allows for better penetration into the hair follicles. Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, clearly the examiner has identified the motivation that would have prompted a skilled artisan to combine an acid to Peck's composition. Thus, a skilled artisan would have been motivated to add an acid to form a minoxidil acid salt for enhanced penetration of minoxidil into the hair follicle.

The second question is whether there is a reasonable expectation of success. In instant case and as set forth in the rejection, Peck teaches the use of minoxidil or a salt thereof. See page 5, lines 25-30. It is known in the pharmaceutical art that the addition of the acid forms a salt and thereby makes the active compound, i.e. minoxidil, more soluble. Hence, the penetration of the

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compound into the skin is increased. Therefore, a skilled artisan would have *reasonably* expected success in adding acid to Peck's composition.

It is incumbent upon the applicant to answer the question "whether the improvement is more than the predictable use of prior art elements according to their established functions", which applicant has not done. It is noted that applicant argues that the addition of a salt increases minoxidil's solubility; thus requiring less co-solvent. However, as discussed above, this is a well known concept in the pharmaceutical art (the addition of the acid forms a salt and thereby makes the active compound hydrophilic and more soluble). Hence, solubilizing the active allows increased penetration of the compound into the skin. This is established by both WO and Yu et al Both WO and Yu teach adding the acid makes it more soluble and increases penetration of minoxidil. In summary, applicant has not shown any unexpected results in rebutting that it is prima facie obvious to combine prior art element to yield a **predictable** result. Further, it should be noted that, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)." Applicant has not provided any factual evidence establishing unobviousness.

Furthermore, the combination of references teaches all the claimed limitations, specifically a composition having both at least 5% minoxidil or a pharmaceutically acceptable salt thereof and less than 10 wt.% polyhydric alcohol. As set forth in the rejection, it is the examiner's position that the recitation of "at least 5%" is rendered obvious by Peck. "At least 5%" includes values such as 5.00001%, 5.001%, etc, which is obvious over the prior art's "5%" since it is conventional to optimize the prior art's range during routine experimentation. Similarly, it is the examiner's position that less than 10% is rendered obvious by Peck. "Less than 10%" includes values 9.9999%, 9.99%, etc., which is obvious over the prior art's 10%.

Applicant argues that Peck teaches away from the instant invention because formulations described in the examples of Peck require high



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percentages of propylene glycol to achieve high minoxidil concentrations. According to applicant, Peck teaches formulations (examples 5 and 6) with both high concentrations of minoxidil, i.e., 5% and high concentrations of propylene glycol, i.e., 50%. Furthermore, applicant argues that Peck does not teach or suggest an advantage of having both reduced levels of polyhydric alcohol (less than 10%) and a high loading of minoxidil (at least 5%). The remarks of the applicant are further supported by the declaration submitted by Barry Hunt. Hunt declares that the compositions in Peck contain a very high percentage of polyhydric alcohol propylene glycol in order to improve the solubility of minoxidil. According to Hunt, such high amounts of polyhydric alcohol are not pharmaceutically or cosmetically elegant and may be unacceptable to the consumer causing local irritation and hypersensitivity upon application to the scalp.

Although the examples are noted, the examiner points out that the instant rejection is made under obviousness and not anticipation. Therefore, the criteria for establishing a case of prima facie obviousness is not whether the prior art exemplifies all the claimed limitations but whether the prior art suggests the claimed limitations. As acknowledged by applicant, Peck teaches a general range of both minoxidil and polyhydric alcohol. This is sufficient in establishing obviousness. Additionally, the examiner directs applicant's attention to MPEP 2123, II: "Disclosed examples and preferred embodiments **do not constitute a teaching away from the broader disclosure** or nonpreferred embodiment".

Moreover, the Rule 132 Declaration under 37 CFR 1.132 by Barry Hunt is insufficient to overcome the rejection of the claims as set forth in the last Office action because:

It is noted that the Declaration provided by Barry Hunt is an opinion Declaration. "Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application." In instant case, the Declaration provided Barry Hunt only provides conclusions

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without any probative value, i.e. evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, etc. It appears the statements are only remarks to the Office Action in a Declaration form. Further, it is noted that Mr. Hunt makes statements such as "may be unacceptable to the consumer, and may cause local irritation" without providing evidence to substantiate such statements. Therefore, the Rule 132 Declaration is unpersuasive.

Applicant argues that the data in Weiner et al clearly illustrates that changing the solubility of minoxidil by reacting it with an acid renders the resultant formulation essentially undeliverable in the absence of encapsulation. Applicant argues that since claims 1 and 112 were amended to recite the transition language "consisting of," it excludes components other than those expressly recited, more specifically the encapsulation in lipid vesicles.

However, the examiner also notes that claims 1 and 112 were also amended to optionally include one or more excipients in the pharmaceutical composition. Therefore, the claims still allow for the addition of lipid vesicles, which could be considered excipients. Since the instant claims are drawn to "penetration enhancers" as excipients, it is noted that lipid vesicles could be considered excipients because the lipid vesicles increase penetration through the skin according to Weiner (pg. 2, line 35 - pg. 3, line 5). In applicant's response, applicant states that Weiner et al teach that the unencapsulated minoxidil formulation does not exhibit improved penetration through the hair follicle and attribute improved penetration to the lipid vesicle and encapsulated minoxidil formulation. Therefore, applicant's response supports the examiner's position that the lipid vesicles of Weiner et al read on the claimed penetration enhancers. The examiner maintains her position in light of the amendment to recite the transition language, "consisting of" because the claim is still optionally drawn to excipients, which can include penetration enhancers.

Applicant argues that Table 1 within Example 3 of Weiner et al teaches away from the lactic acid salt addition.

The examiner notes that WO 97/12602 teaches Formula III has "twice the penetration" than any other formula as disclosed by Weiner on page 7, lines 9-11. Commercial Rogaine has the "next best" penetration. Formula III comprises a vesicle material, lactic acid, ethanol, and minoxidil. The Rogaine formulation comprised minoxidil, ethanol, water, and propylene glycol. Thus, as acknowledged by applicant, Formula III wherein the minoxidil is made hydrophilic by the addition of an acid and encapsulated has better skin penetration. As discussed above, the instant claims do not exclude the lipid vesicle. Therefore, Weiner does provide the motivation to combine the references. Moreover, Weiner clearly establishes that a polyhydric alcohol is not required to increase penetration since Formula III does not have a polyhydric alcohol. Therefore, it is reasonable to expect that the minimum range taught by Peck could be utilized since the lipid vesicle and acid addition salt to help increase penetration of minoxidil.

Moreover, the examiner points out that Weiner's comparison of Formula XI and commercial Rogaine is not a proper comparison that can be applied to the instant invention for the following reasons: The commercial Rogaine formulation comprises minoxidil, ethanol, water, and propylene glycol. Formula XI comprises lactic acid, minoxidil, and ethanol. However, this formulation does not comprise a glycol, which is a known penetration enhancer. Thus, obviously Rogaine would function better since it has two penetration enhancing agents (acid and a glycol) compared to Formula XI, which has one (acid). Therefore, one cannot conclude that adding an acid alone does not and cannot increase the penetration of minoxidil since both formulations in WO are not controlled with only one variable. Meaning, the same formulations containing the same excipients/carriers should have been compared, wherein minoxidil was the only variable, i.e. the minoxidil versus its acid addition salt. Other variables in the Rogaine formulation, i.e. propylene glycol, affected the penetration of minoxidil. Therefore, this argument does not show the unobviousness of the invention.

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Applicant argues that increased solubility is not equivalent to increased skin permeation.

The examiner agrees that this phenomenon does not apply to all drugs. However, in the instant case, it clearly applies to minoxidil. This is established by Weiner and Yu et al as discussed in the preceding paragraphs.

Applicant argues that Yu only teaches a 2% minoxidil formulation and a large polyhydric content. In addition, applicant argues that the use of an acid addition salt is negated by Weiner (WO 97/12602). According to the applicant, Yu et al does not teach or suggest a composition having both at least 5% minoxidil and less than approximately 10% by weight polyhydric alcohol.

First, the argument that WO negates the use of an acid addition salt has been addressed above. As discussed above, WO does not negate the use of an acid addition salt since it is not a proper comparison to commercial Rogaine. Second, the examiner notes that applicant argues against the references individually. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the examiner's position that Peck renders instant recitation "at least 5% minoxidil" and "less than 10%" obvious and thus Yu et al is not relied upon to cure this deficiency. Yu et al is merely relied upon to provide motivation to utilize an acid to form a salt, which is also suggested by Peck.

Therefore, it is the examiner's position that the instant claims are rendered obvious over Peck et al in view of Weiner or Yu et al.

**Claims 14, 30-33, 36-40, 43-44, 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 88/01863 to Peck et al in view of WO 97/12602 or Yu et al (EP0273202) respectively in further view of Uchikawa et al (5,156,836).**

The teachings of Peck, Yu, and WO '602 have been set forth above.

Peck does not teach the elected glycerol co-solvent or the use of an antioxidant.

Uchikawa teaches a hair revitalizing composition that may comprise minoxidil. Uchikawa teaches conventional excipients used to formulate hair-revitalizing compositions include polyhydric alcohols such as glycerine and propylene glycol, antioxidants, etc. see column 4, lines 5-30.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and substitute the exemplified propylene glycol with the instantly claimed glycerol and arrive at the instant invention. One would have been motivated to do so since Uchikawa teaches both propylene glycol and glycerol are polyhydric alcohols conventionally used in the art. Therefore, a skilled artisan would have expected similar results absent unexpected results by using any conventional polyhydric alcohol known in the art in the composition. Further, it would have been obvious for a skilled artisan to further utilize a conventional excipient such as an antioxidant as taught by Uchikawa to prevent oxidation.

### ***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues the merits of Peck et al, WO, and Yu et al and argues that claims 1, 21, and 112 have been amended to recite the transition language "consisting of." Applicant argues that this transition language excludes lipid vesicles.

These arguments have been addressed above and are incorporated herein.

Furthermore, applicant argues that Uchikawa does not teach or suggest an acid salt. However, this argument is unpersuasive since it is the examiner's position that WO and Yu et al cure this deficiency and Uchikawa is only relied upon to teach the instant co-solvent.

Therefore, it is the examiner's position that the instant claims are rendered obvious over Peck et al in view of WO 97/12602 or Yu et al in further view of Uchikawa.

**Claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 112, 118-125, 128, 131-132, 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 07-048230 in view of WO 97/12602 or Yu et al (EP0273202) respectively in further view of Caldini et al (4,272,516).**

JP '230 teaches a hair tonic with hair restoring properties comprising 0.1-10g minoxidil, 30-70g ethanol and water. See abstract.

JP does not specifically teach adding an acid or a cosolvent.

WO teaches a topical composition for minoxidil and teaches minoxidil is not soluble in water, acetone, ethyl acetate and although the alcohol based solutions of minoxidil have only some penetration. See page 2. WO teaches modifying the solubility of the active in an aqueous solution by making it more hydrophilic without changing the active agent's therapeutic properties. The active agent that is more hydrophilic, has improved penetration through the hair follicle. WO teaches modifying by the pH reacting it with a hydroxy organic acid such as lactic acid. See page 3 and 4.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help the minoxidil dissolve in the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

Caldini et al teach a process for improving transcutaneous and transfollicular absorption of cosmetic compositions in the amount of 5-33.33%. See abstract. Caldini teaches benzyl alcohol has the ability of facilitating the absorption of the other components through the skin and its associated organs.

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See column 1, lines 10-20. The cosmetic compositions include a lotion for reactivating the hair, a reactivating jelly, a tonic milk, and a reactivating cream. See column 4, lines 40-45. **Caldini teaches a reactivating lotion for the hair that comprises comprising a solvent system of 4% propylene glycol, 12% benzyl alcohol, 31.5% water, and 47.5% ethanol. See example 1.** Both PPG and benzyl alcohol read on the co-solvent. Further, benzyl alcohol reads on the penetration agent.

It is would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of JP and WO and utilize the instant minoxidil acid salt. One would have been motivated to do so since WO teaches this addition to yield a hydrophilic compound, allows for better penetration into the hair follicles. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teaching of JP and Yu et al and utilize the instant acid. One would be motivated to do so since Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid for enhanced penetration of minoxidil into the hair follicle.

It would have been obvious at the time the invention was made to combine the teachings of the above references and utilize benzyl alcohol in the solvent system. One would have been motivated to do so since Caldini et al teach the use benzyl alcohol in an amount of 5-33.33% improves transcutaneous and transfollicular absorption of active agents, especially hair reactivating composition. Thus one would expect an additive effect of increasing penetration of the composition by adding benzyl alcohol in JP's composition.

Regarding the instantly claimed ratio of ethanol to water, JP teaches 30-70g ethanol and water and this sets forth a general range of components. Thus, it is within the skill of an artisan to look at the guidance provided by JP and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally a difference in concentrations do not support the patentability of subject matter

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encompassed by the prior art unless there is evidence indicating such as concentration is critical.

### ***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues against the merits of Weiner et al and Yu et al and the amendment regarding the transition language of claims 1, 21, and 112. Each of these arguments have been addressed and incorporated herein.

Applicant argues that Caldini does not cure the deficiencies of addition of an acid. Caldini is only relied upon to teach the co-solvent and applicant has not addressed this.

Thus, it is the examiner's position that JP in view of Weiner et al or Yu et al in further view of Caldini et al renders the claims as amended obvious.

**Claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al.**

Navarro teaches the solvent system comprising the combination of ethanol or isopropyl alcohol and propylene glycol or polyethylene glycol solubilize minoxidil but the significant amount of propylene glycol makes the hair greasy and shiny. See page 2 of translation. Navarro teaches using cyclodextrin to reduce the amount of solvent required to solubilize minoxidil. See page 3 of the translation. Navarro teaches a hair care composition containing 0.1-7% minoxidil, 0.1-5% cyclodextrin, 0.5-15% minoxidil solvent (propylene glycol), 30-50% monoalcohol (ethanol or isopropanol), and water. Note abstract and examples.

Navarro does not teach the use of lactic or acetic acid.

Weiner teaches a topical composition for minoxidil. WO discloses that making materials more hydrophilic, improves penetration through the hair follicle.



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Weiner teaches that a number of different modifications may be made to the minoxidil. One such modification is provided by reacting minoxidil with an organic acid such as lactic acid. The minoxidil may also be converted to a salt by reacting it with a cyclodextrin. See page 3. Weiner states that the use of a minoxidil acid salt addition provides substantial penetration and cyclodextrin salt addition is the "next best". See page 7. Weiner teaches encapsulation of minoxidil increase penetration of the active across the skin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Navarro et al and Weiner et al and substitute Navarro's cyclodextrin with the instant acid to convert minoxidil into a salt. One would be motivated to do so since Weiner teaches that by converting minoxidil to a hydrophilic compound, it penetrates the skin. More specifically, Weiner teaches the conversion of minoxidil into a salt form by reacting it with an organic acid such as instant lactic acid or with cyclodextrin and notes that although both provide penetration of minoxidil, the acid salt addition has a better effect than the cyclodextrin salt addition. Therefore, one would have been motivated to use an acid salt addition to convert minoxidil into a hydrophilic compound rather than Navarro's cyclodextrin since Weiner teaches the acid salt addition has better penetration into the skin. With regard to the pH recited in the dependent claims, it is the examiner's position that the combination of Navarro and Weiner would yield a pH since the lactic acid would render a pH in the acidic range. The examiner cites Yu et al (EP '202) to support this position wherein lactic acid and minoxidil yield a composition with a range of 4.6.

With regard to the instantly claimed ratio, Navarro sets forth a general range of components wherein a monoalcohol is utilized in an amount of 30-50% and water to balance, thus it is within the skill of an artisan to look at the guidance provided by Navarro and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is

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evidence indicating such as concentration is critical. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regard to claim 4, the lower limit of *approximately* 7.5% is considered obvious over Navarro's teaching that the minoxidil may be in the amount of 7%. A skilled artisan would have been motivated to manipulate the concentration of active, i.e. increase the amount of minoxidil, in the composition depending on the desired "strength" of the composition.

Note that the hair tonic reads on the elected species "spray" since the composition is capable of being sprayed.

### ***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues that since claims 1 and 21 were amended to recite the transition language "consisting of," it excludes components other than those expressly recited, more specifically the encapsulation in lipid vesicles or in a cyclodextrin carrier. According to applicant, Navarro et al does not teach or suggest a formulation absent a cyclodextrin carrier.

However, the examiner notes that claims 1 and 21 were also amended to optionally include one or more excipients in the pharmaceutical composition. Therefore, the claims still allow for the addition of lipid vesicles or cyclodextrin carriers, which could be considered excipients.

In addition, applicant argues that cyclodextrin and minoxidil have a host-guest configuration that imparts the solubility properties. Applicant argues that cyclodextrin is unstable in an acid environment. Applicant provides a Rule 132 Declaration by Mr. Abram to substantiate this argument.

The examiner acknowledges Mr. Abram's Declaration that cyclodextrin and minoxidil have a host-guest configuration, which imparts the solubility properties. The examiner notes that that cyclodextrin is unstable in an acid environment, which would "destroy" its ability to solubilize the drug. However, the

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premise of the rejection is to substitute cyclodextrin with instant acids. The premise is not to add an acid to Navarro's composition. Further, the examiner points out that the fact that cyclodextrin and acids have different mechanisms of imparting solubility to a drug, both still act to solubilize a drug.

Furthermore, applicant argues against the merits of Weiner et al. These arguments have been addressed and are incorporated herein.

Therefore, it is the examiner's position that the instant claims are rendered obvious over Navarro et al in view of Weiner et al.

**Claims 14, 30-33, 36-40, 43-44, 112, 118-125, 128, 131-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al in further view of Wong et al (5,130,142).**

The teachings of Navarro and Weiner have been set forth above.

The references do not teach the elected glycerol cosolvent or a propellant.

Wong teaches a hair growth formulation. Wong teaches a composition in solution form can be applied to the skin as is, or else can be formulated into an aerosol and applied to the skin as a spray-on. To formulate an aerosol composition, a suitable propellant is used to expel the contents of the container. See column 9, lines 10-15 and column 12, lines 16-25. Further, Wong teaches solvents include glycerol, propylene alcohol, polyethylene glycol, butanediol are solvents. Other conventional excipients include antioxidants and emulsifiers. Wong teaches the use of skin emollients including cetyl alcohol.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and further utilize a propellant. One would have been motivated to do so if one desired administering the solution as a spray-on since Wong teaches a propellant allows a solution to aerosolize (expel from the container). Further, it would have been obvious to use either propylene glycol or glycerol and arrive at the instant invention. One would have been motivated to do so since Wong

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teaches both are solvents conventionally used in the art. Further, a skilled artisan would have expected similar results absent unexpected results since both are polyhydric alcohol. Additionally, the use of a conventional excipient such as an antioxidant, emulsifiers, and emollients would have been obvious to an artisan of ordinary skill. One would have been motivated to add an antioxidant if one desired to prevent oxidation. Lastly, it would have been obvious to utilize cetyl alcohol (reads on penetration enhancer and higher alcohol) for its emollient properties as taught by Wong.

### ***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues that Wong does not cure the deficiency of Navarro and Weiner and argues that claims 1 and 21 have been amended to recite the transition language "consisting of." Applicant argues that this transition language excludes lipid vesicles and/or in a cyclodextrin carrier.

The merits of Navarro and Weiner have been discussed above and incorporated herein. Wong is only relied upon to teach the co-solvent and a propellant, which applicant has not addressed.

In addition, the examiner notes that claims 1 and 21 were also amended to optionally include one or more excipients in the pharmaceutical composition. Therefore, the claims still allow for the addition of lipid vesicles or cyclodextrin carriers, which could be considered excipients.

Thus, it is the examiner's position that Navarro in view of Weiner et al in further view of Wong et al renders the claims as amended obvious.

**Claims 30-31, 36-40, 43-44, 112, 114, 118-125, 128, 131-132, 135-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/03638 to Navarro et al in view of WO 97/12602 to Weiner et al in further view of WO 88/01863 to Peck et al.**

The teachings of Navarro and Weiner have been set forth above.

The references do not teach the instant excipients claimed in independent claim 30 (propellant, a higher alcohol, antioxidant, and stabilizer) or independent claim 112 (specific skin penetration enhancers).

Peck teaches a quick breaking foam to treat alopecia (loss of hair on the scalp) comprising either (a) 1-5% minoxidil; (b) 10-50% propylene glycol; (c) 30-75% alcohol; (d) 0.5-10% emulsifier and/or surfactant; (e) 0.1-5% hydroxypropylmethylcellulose; and (f) 10-50% water wherein the composition is actuated with a propellant. See page 2. Peck teaches the minoxidil may be selected from any known analog. Peck teaches skin penetrating enhancers including alcohol such as dodecanol and oleyl alcohol. See page 5. Peck teaches various surfactants in the composition including Tween 80 (polysorbate) and Span 60 to improve the stability of the composition. See page 6, lines 20-25. Peck teaches the use of minoxidil or a salt thereof. See page 5, lines 25-30. The method of making the composition is taught in the examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and further utilize the instant excipients. One would have been motivated to utilize a propellant, if one desired administering the solution as a spray-on since Peck teaches a propellant allows a solution to aerosolize (expel from the container). Second, it would have been obvious to utilize instant higher alcohols since Peck teaches the use of dodecanol and oleyl alcohol to increase skin penetration of minoxidil. Thus, a skilled artisan would have been motivated to further add a higher alcohol to provide an additive affect of enhancing the penetration of minoxidil thorough the skin. Third, it would have been obvious to utilize a surfactant such as those taught in Peck since Peck teaches various surfactants stabilize compositions. Thus, one would have been motivated to add a surfactant to increase stability of the composition.

***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues that Peck et al does not cure the deficiencies of Navarro and Weiner and argues that claims 1 and 21 have been amended to recite the transition language "consisting of." Applicant argues that this transition language excludes lipid vesicles and/or in a cyclodextrin carrier.

The merits of Navarro and Weiner have been discussed above and incorporated herein. Peck et al is only relied upon to teach the instant excipients, which applicant has not addressed.

In addition, the examiner notes that claims 1 and 21 were also amended to optionally include one or more excipients in the pharmaceutical composition. Therefore, the claims still allow for the addition of lipid vesicles or cyclodextrin carriers, which could be considered excipients.

Thus, it is the examiner's position that Navarro in view of Weiner et al in further view of Peck et al renders the claims as amended obvious.

**Claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bazzano (5183817) in view of WO 97/12602 or Yu et al (EP0273202) respectively.**

Bazzano teaches a minoxidil composition to increase growth rate and stimulate new hair growth by administering a lotion containing 0.01-0.1% retinoic acid or its ester (note this reads on penetration enhancer), 0.5-5% minoxidil, ethanol, 5-50% propylene glycol, 0.1% BHT, and distilled water (up to 10%). Formulation example II contains 1% retinoic acid, 10% minoxidil, 4% cetyl alcohol, 4% ethanol, and up to 100% water. Bazzano teaches the use of pharmaceutically acceptable acid salt. See column 19, lines 1-25. Bazzano states that minoxidil or its derivatives and analogs that are described in US patents 5910928, 3637697, 3461461, 4139619, and 4596812 are incorporated into the reference. US patent 3,461,461 teaches the acid salt derivatives

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including lactic acid and other instantly claimed acids of minoxidil. Bazzano discloses that a major problem in influencing hair growth is obtaining good percutaneous absorption of the active compounds. The retinoid compounds cause excellent absorption of the hair follicles. See column 19, lines 35-40. The formulation can contain any pharmaceutically acceptable carrier, additive, or solubilizer.

Although Bazzano states that a minoxidil derivative/analog may be utilized, Bazzano does not explicitly teach the use of an acid addition.

WO teaches a topical composition for minoxidil and teaches minoxidil is not soluble in water, acetone, ethyl acetate and although the alcohol based solutions of minoxidil have only some penetration. See page 2. WO teaches modifying the solubility of the active in an aqueous solution by making it more hydrophilic without changing the active agent's therapeutic properties. The active agent that is more hydrophilic, has improved penetration through the hair follicle. WO teaches modifying by reacting it with an hydroxy organic acid such as lactic acid. See page 3 and 4.

Yu et al teach additives such as hydroxy acids enhance the therapeutic effects of pharmaceutical and cosmetic actives in topical treatments. See page 2. The pharmaceutical or cosmetic active is utilized generally in the amount of 0.01-40% and the hydroxyl acid is used in the amount of 0.01-99%. See page 6. Yu teaches the use of 3% lactic acid with minoxidil to help the minoxidil dissolve in the solution and enhance penetration and the efficacy of minoxidil on hair growth. The pH of the solution is 4.7. See example 3.

It is would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bazzano and WO and utilize the instant minoxidil acid salt. One would have been motivated to do so since WO teaches this addition to yield a hydrophilic compound, allows for better penetration into the hair follicles. Further, since Bazzano is concerned with penetration of the composition into the hair follicle one would expect an additive effect of increasing penetration of the composition by adding instant salt. A

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skilled artisan would have reasonably expected success and similar results since Bazzano also teaches the acid salts may be utilized and incorporated other US patents wherein the instant acid salt is taught.

Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made combine the teaching of Bazzano and Yu et al and utilize the instant acid. One would be motivated to do so Yu teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil. Therefore, a skilled artisan would have been motivated to add an acid for enhanced penetration of minoxidil into the hair follicle. Moreover, one would have expected similar results by the instant combination since Bazzano suggests the use of an acid addition salt.

Regarding the instantly claimed ratio, Bazzano sets forth a general range of components wherein water is utilized in an amount up to 10% and ethanol is to balance, thus it is within the skill of an artisan to look at the guidance provided by Bazzano and manipulate the concentrations (ratio) of water and ethanol depending on the concentration of the other components. It should be noted that generally difference in concentrations do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such as concentration is critical. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

### ***Response to Arguments***

Applicant's arguments filed 6/20/08 have been fully considered but they are not persuasive.

Applicant argues the merits of Weiner et al or Yu et al and argues that claims 1 and 21 have been amended to recite the transition language "consisting of." Applicant argues that this transition language excludes lipid vesicles.

The merits of Navarro and Weiner/Yu have been discussed above and incorporated herein.



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In addition, the examiner notes that claims 1 and 21 were also amended to optionally include one or more excipients in the pharmaceutical composition. Therefore, the claims still allow for the addition of lipid vesicles or cyclodextrin carriers, which could be considered excipients.

Thus, it is the examiner's position that Navarro in view of Weiner et al or Yu et al renders the claims as amended obvious.

The rejection of claims 1-4, 6, 8, 12-13, 15-16, 19, 20-21, 23-24, 26, 29, 30-31, 36-37, 39-40, 43-44, 112-113, 118-125, 128, 131-132, 135-136, 138 as being rendered obvious over Di Schiena (4866067) in view of Yu et al (EP0273202) is **withdrawn** in light of the amendments.

### ***New Rejections***

The following rejection constitutes a new grounds for rejection necessitated by amendment.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 21, 30, and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to minoxidil or a pharmaceutically acceptable salt thereof selected from the group consisting of minoxidil acetate, minoxidil citrate, etc. However, the claims also recite an acid to completely solubilize the minoxidil which include hydrochloric acid, sulfuric acid, etc. The acids in the claim are identical to the salts of the minoxidil that would be made if the minoxidil and acid were combined. Therefore, there is a redundancy in the claims and the recitation

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of **both** pharmaceutically acceptable salts of minoxidil and acids used to solubilize minoxidil is unnecessary.

### ***Conclusion***

No claims are allowed. Claims 1-4, 6, 8, 12-16, 19-21, 23-24, 26, 29-33, 36-40, 43-44, 112, 114, 118-125, 128, 131-133, 135-138 are rejected.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/

Primary Examiner, Art Unit 1611